REMARKS

With this response, claims 1-20 are pending. Claims 1, 4-7, and 9-11 have been amended without prejudice, and new claims 14-20 have been added by way of the present amendment. Support for the amendments and new claims can be found throughout the specification and the claims as originally filed. For instance, support for the claim amendment "an amino acid sequence that is more than 30 amino acid residues in length" can be for, *e.g.*, at page 28, line 30 to page 29, line 2 of the specification. Support for the claim amendments and new claims regarding SEQ ID NOs: 47 and 48 can be found, *e.g.*, in the description of compounds of Formula VII and VIII on pages 42-46 of the specification. Support for the claim amendments and new claims regarding polymer-modified exendins and polymer-modified exendin analogs can be found, *e.g.*, at page 50, lines 9-25 and Example 6. Support for the claim amendments regarding exendin analogs can be found, *e.g.*, at page 19, lines 16-19 and Figures 3 and 4. Additional support for such amendments and new claims will be apparent to one of skill in the art.

I. Information Disclosure Statement

Initially, it is noted that the Examiner-initialed copy of the PTO-1449 form submitted by Applicant on January 3, 2002 and returned by the Examiner with the Office Action mailed July 16, 2002, includes both Examiner initialing indicating consideration of certain cited references and lining thorough indicating that the cited references were not considered. Clarification is requested. If additional copies of references are required, please advise.

II. Objection to the Claims

Claim 11 has been objected to due to the recitation of "in dosage unit form" rather than "in a dosage unit form." Without agreeing that such a qualifier is required, Applicant has amended claim 11 as suggested by the Examiner. However, such amendment does not narrow the scope of the claim.

III. Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1, 7-8 and 9-10 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabling one of skill in the art to make and/or use the invention. This rejection is respectfully traversed for at least the reasons which follow.

The Examiner acknowledges that the specification is enabled for conjugating PEG polymers to exendin-4, and for the use of exendin peptides in suppressing and/or lowering glucagon secretion in patients having Type II diabetes. *Office Action, Paper No. 17* at page 2. However, the Examiner asserts that that specification "does not reasonably provide enablement for using the *PEG-modified* exendin-4 conjugates to treat glucagonoma syndrome that is characterized by a necrolytic migratory erythematous rash." *Id.* at page 3 (emphasis in original). More particularly, the Examiner states that:

> The specification establishes the method of preparation [sic] exendin and the PEG-modified exendin mediated peptides, shows a decrease of plasma glucagon mediated by the peptides, and sets forth example for [sic] effect of the exendin peptide on glucagon secretion in patients with type II diabetes.

Id. at page 4.

However, in support of the rejection, the Examiner alleges that:

> the specification is silent as to a therapeutic relation of lowering glucagon secretion by the PEG-modified exendin to the disease states: glucagonoma and glucagonoma-related necrolytic migratory erythema.

Id.

Applicant respectfully traverses this rejection. Initially, it is submitted that the Examiner has not met the evidentiary burden to impose an enablement rejection for failure to enable one of skill to use the invention. A specification that discloses how to make and use a claimed invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented "must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995) (*quoting In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA. 1971) (emphasis in original)).

Applicant has provided considerable direction and guidance, and has presented working examples such that it is well within the level of ordinary skill in the art to practice the invention without undue experimentation. The Examiner has not provided sufficient evidence to cast doubt on the guidance provided in the specification. Rather, the Examiner has provided generalizations regarding unpredictability in the art and the need for some experimentation to determine "therapeutic parameters."

Even assuming, *arguendo*, that the Examiner's generalization regarding the unpredictable state of the art is accepted, the conclusion that undue experimentation would be required is inconsistent with the current state of the law. Specifically, the law provides that experimentation is not necessarily undue simply because it is complex, if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174, (Int'l Trade Comm'n 1983) *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985).

For instance, based on the guidance provided in the specification regarding the therapeutic activity of exendins, the mechanism of *in vivo* clearance of exendins, and the coupling of polymer-moieties to exendins and exendin analogs, it is well within the level of ordinary skill in the art to design therapeutically active polymer-modified exendins and exendin analogs without the need for undue experimentation. More particularly, Examples 4 and 5 confirm the ability of exendin-4 to decrease glucagon secretion *in vivo*. Additionally, Example 3 illustrates that kidney filtration is primarily responsible for the *in vivo* clearance of exendin-4. Based on this clearance mechanism, it is further disclosed that modifications to exendins that increase their size and/or anionic nature will decrease their ability to be filtered by the kidney, and will therefore increase their *in vivo* half-life. Example 6 then goes on to provide extensive details and considerations for modifying exendins with polymers such that the exendins retain their therapeutic activity. Based on such guidance, one of skill in the art would be able to practice the claimed invention with only routine experimentation.

Moreover, contrary to the Examiner's allegation that the specification is silent with regard to the therapeutic relation of the PEG-modified exendins to the specified disease states, the specification does provide guidance as to the therapeutic relation. For instance, as mentioned

above, Example 6 provides guidance regarding the design of polymer-modified exendin compounds, detailing considerations for retaining therapeutic activity. Further, the specification discloses that glucagonoma and necrolytic migratory erythema respond to glucagonostatic agents, and that the presently claimed exendin compounds are glucagonostatic agents. *Specification*, page 7, lines 32-33. Further, based on the Examiner's argument with respect to the prior art rejections, discussed *infra*, "[b]eause glucagonoma and necrolytic migratory erythema are featured by abnormally elevated glucagon," compounds which "suppress glucagon *via* inhibiting glucagon secretion" are useful in treating such diseases. *Office Action, Paper No. 17* at page 14. As such, the specification does provide for a therapeutic relation between polymer-modified exendin compounds and the specified disease states.

An analysis of the *In re Wands* criteria also supports Applicant's position that no undue experimentation would be required to make and use the claimed invention. *See In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1998). The first *Wands* criterion is the quantity of experimentation necessary. The "make-and-test" quantum of experimentation is reduced by the extensive knowledge to which a person of ordinary skill in the art has access, *e.g.*, various mechanisms for coupling polymers to peptide molecules, and the effects of glucagonostatic agents of disease states characterized by elevated glucagon levels. Performing routine and well-known steps, such as polymer modifications and activity assays, cannot create undue experimentation, even if it is laborious. *See In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 218-219 (CCPA 1976).

The second and third *Wands* criteria relate to the amount of direction or guidance given, and the presence or absence of working examples. As discussed above, the present specification provides ample guidance and direction in the form of the identification of a representative number of specific exendin analogs and polymer-modifications to exendin compounds, methodologies to prepare such exendin analogs and polymer-modified exendin compounds, conditions to verify exendin molecule activity, and working examples demonstrating all of the above.

The fourth, fifth, and sixth *Wands* criteria focus on the nature of the invention, the state of the art, and the relative skill in the art. The present invention relates to methods for lowering

plasma glucagon in a subject by administering exendin compounds. Considerable knowledge and resources guide practitioners in this art as to the conditions and approaches that can be utilized to prepare and assay such compounds. Many resources are readily available to the skilled art worker. Moreover, as discussed above, the present specification itself adds to the relative skill in the art by providing detailed guidance regarding the application of such techniques to the art of the present invention. Such resources, combined with the specification and the general knowledge of those skilled in the art provide ample guidance to enable one of ordinary skill in the art to make and use the claimed invention.

The seventh criterion considers the predictability of the art. The Examiner alleges that the claimed invention "involves highly variant PEG-modified exendin conjugates" and that the outcome of administering such conjugates is "unpredictable in the absence of factual indicia to the contrary." *Office Action, Paper No. 17* at page 6. The Examiner appears to rely on the concept that "different diseases require different therapeutic procedures and protocols as well as doses and forms of pharmaceutics." *Id.* Even assuming, *arguendo*, that such a concept is accurate, determination of such procedures and protocols is well within the level of skill in the art once a candidate glucagonostatic agent is identified. Further, it is submitted that the specification discloses sufficient guidance to render the results predictable within the context of the exendin compounds of the invention. In fact, by providing guidance as to the selection of exendin compounds, the design of polymer-modifications to such exendin compounds, and the demonstration of glucagonostatic activity consistent with such guidance, Applicant has demonstrated that the present invention yields a predicted result.

The eighth criterion focuses on the breadth of the claims. Enablement is satisfied when the disclosure "adequately guide[s] the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility." *In re Vaeck,* 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991). In the present case, one of skill in the art is specifically guided by the disclosure to look to specific polymer-modification design considerations, and is provided sufficient methodology to prepare exendin compounds and to verify activity of such compounds. As such, based on the teachings of the specification, one of skill in the art would be able to ascertain which species possess the

disclosed utility and thus fall within the scope of the claims. It is thus submitted that the specification provides enablement commensurate in scope with the claims.

Accordingly, for at least these reasons, it is submitted that the claims are sufficiently enabled under 35 U.S.C. § 112, first paragraph, and withdrawal of this rejection is respectfully requested.

IV. Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 1-13 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. It is submitted that the present claims are definite in scope, and withdrawal of this rejection is respectfully requested.

Claim 1 and the claims dependent thereon stand rejected as allegedly indefinite in that the difference between an exendin and an exendin agonist is unclear. This rejection is respectfully traversed. It is submitted that one of skill in the art would be appraised of the scope of the claim. However, in order to facilitate prosecution, the claims have been amended to recite exendins and exendin analogs. As such, any alleged overlap between the claim terms has been clarified. As such, withdrawal of this rejection is respectfully requested.

The Examiner also asserts that Claim 1 is indefinite due to the recitation of an improper Markush group. The claims have been amended to recite proper Markush terminology where appropriate. However, such amendment does not narrow the scope of the claims. As such, withdrawal of this rejection is respectfully requested.

Finally, the Examiner asserts that Claim 1 is unclear due to the recitation of the terms modified exendin and modified exendin agonist. This rejection is respectfully traversed. It is submitted that, based on the teachings of the specification, one of skill would clearly understand the term modified exendin and modified exendin agonist. However, to expedite prosecution, the claims have been amended to recite polymer-modified exendin and polymer-modified exendin analog. As such, withdrawal of this rejection is respectfully requested.

Claim 6 stands rejected as allegedly indefinite due to the recitation of "any of claims 1-3 or 4". Claim 6 has been amended to recite "any of claims 1-3." As such, it is submitted that claim 6 complies with 35 U.S.C. § 112, second paragraph, and withdrawal of this rejection is respectfully requested.

Claim 7 stands rejected as allegedly indefinite due to the recitation of "modified exendin . . . is linked to one or more polyethylene glycol (PEG) polymers." This rejection is respectfully traversed. Based on the teachings of the specification, it is submitted that one of skill in the art would clearly understand the meaning and scope of the claim limitation. Nonetheless, in order to facilitate prosecution, the claims have been amended to recite modified exendins comprising an exendin linked to one or more polyethylene glycol polymers. As such, withdrawal of this rejection is respectfully requested.

Claim 10 stands rejected as allegedly indefinite due to the recitation of "at least one of an exendin, . . ." This rejection is respectfully traversed. It is submitted that one of skill in the art would clearly understand the meaning and scope of the claim limitation. Nonetheless, in order to facilitate prosecution, claim 10 has been amended to recite that the composition consists essentially of an exendin, an exendin analog, a polymer-modified exendin, a polymer-modified exendin analog, or combinations thereof. However, such amendment does not narrow the scope of the claim. As such, withdrawal of this rejection is respectfully requested.

IV. Rejection under 35 U.S.C. § 102

A. U.S. Patent No. 5,424,286 to Eng *et al.*

Claims 1-6 and 9-13 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,424,286 to Eng *et al* ("Eng"). In support of this rejection, the Examiner asserts that:

> Eng teaches that glucagon-like insulinotropic peptide (GLIP) significantly lowers the plasma concentrations of insulin and glucagon . . ., and teaches that, like GLIP, exendin-4 acts as an insulinotropic agent. Thus, lowering plasma glucagon in a subject is inherent in the patent. . . Since glucagonoma and necrolytic migratory erythema are associated with elevated plasma glucagon level [sic], claims 2 and 3 are also included in the rejection.

Office Action, Paper No. 17 at page 14.

This rejection is respectfully traversed for at least the reasons which follow. It is well established that to anticipate a claim, a reference must disclose every element of the claim. *Verdegaal Bros. v. Union Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). The

identical invention must be shown in complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989).

Applicant respectfully submits that the method disclosed by Eng does not include all of the limitations of the present claims. Initially, Eng fails to teach, disclose, or suggest the ability of exendins to lower glucagon levels. The only mention of glucagon levels in Eng is in reference to the ability of GLIP to lower meal-related increases in plasma concentrations of glucagon. However, there is no discussion of the ability of disclosed exendins in this regard. Further, Eng fails to disclose or suggest the benefits of the therapeutic lowering of glucagon levels, much less the identification of a subject in need of lowering of glucagon levels. The passing reference in Eng to the ability of GLIP to lower meal-related increases in plasma concentrations of glucagon does not disclose or suggest the need for the lowering of glucagon levels. Moreover, as discussed above, there is no teaching in Eng to suggest the ability of the disclosed exendins to lower glucagon levels, much less a disclosure of therapeutic glucagon lowering amounts of such exendins.

As such, Eng does not teach, inherently disclose, or suggest the therapeutic lowering of glucagon levels in a subject, such as a subject suffering from glucagonoma and necrolytic migratory erythema, by administering an exendin. Rather, the disclosure of Eng is directed specifically to the insulinotropic activity of specific exendins. Although there is a suggested comparison of the disclosed exendins to GLIP with regard to insulinotropic activity, there is no indication in the prior art of record that the disclosed exendins would act in a manner similar to that of GLIP with regard to glucagonostatic activity.

In sum, whatever else Eng does teach, it does not disclose the presently claimed invention. For at least these reasons, it is respectfully submitted that Eng does not anticipate the present claims. Therefore, reconsideration and withdrawal of this rejection is respectfully requested.

B. Marketletter, published 24 August 1998

Claims 1-6 and 9-13 also stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Marketletter, published 24 August 1998. This rejection is respectfully traversed for at least the reasons which follow.

Initially, it is submitted that Marketletter is not available as prior art, as the citation does not reflect activity "by another." Marketletter states that Amylin (*i.e.*, Amylin Pharmaceuticals, Inc.) is engaged in clinical trials investigating the use of exendin-4 in the treatment of type 2 diabetes. It is noted that Amylin Pharmaceuticals, Inc. is the assignee of the present application. As such, the work described in Marketletter is that of the Applicant. This disclosure of Applicant's own work is therefore not available as prior art under 35 U.S.C. §102(a).

Nonetheless, even assuming *arguendo* that Marketletter is available as prior art, Marketletter merely discusses the effects of exendin-4 on insulin secretion and plasma glucose levels. Marketletter does not disclose, teach, or suggest the ability of exendin-4 to lower glucagon levels. As discussed above with reference to Eng, the passing reference in Marketletter concerning inhibition of glucagon secretion refers to the activity of glucagon-like peptide-1 (*i.e.*, GLIP). Again, although there is a suggested comparison of exendin-4 to GLIP with regard to insulinotropic activity, there is no indication in the prior art of record that exendin-4 would act in a manner similar to that of GLIP with regard to glucagonostatic activity.

In sum, it is submitted that Marketletter is not available as prior art. Even assuming, arguendo, that it is prior art, it is respectfully submitted that Marketletter does not anticipate the present claims. Therefore, reconsideration and withdrawal of this rejection is respectfully requested.

V. Rejection under 35 U.S.C. § 103

Claims 1 and 4-8 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Marketletter, taken in combination with U.S. Patent No. 6,051,557 to Drucker ("Drucker"), WO 98/30231 to Young *et al.* ("Young"), and U.S. Patent No. 4,179,397 to Frank ("Frank"). This rejection is respectfully traversed for at least the reasons which follow.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The teaching or suggestion to make the claimed combination must be found in the prior art, and not be based on Applicant's disclosure. *See* M.P.E.P. §§2143.01 and 2143.03.

Initially, as discussed above, it is submitted that Marketletter is not available as prior art. Nonetheless, even assuming *arguendo* that Marketletter is prior art, Drucker, Young, and Frank do nothing to provide a teaching or suggestion as to the benefits of the therapeutic lowering of glucagon levels or the glucagonostatic activity of exendins, exendin analogs, polymer-modified exendins, or polymer-modified exendin analogs.

In sum, Applicant respectfully submits that the cited references do not render the present claims obvious, since significant limitations of the claims are neither taught nor suggested by the cited references. As such, withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the above, each of the presently pending claims is believed to be in immediate condition for allowance. All of the stated grounds of objection and rejection have been traversed, accommodated, or rendered moot. Accordingly, the Examiner is respectfully requested to withdraw the outstanding objections and rejections of the claims, and to pass this application to issue. The Examiner is encouraged to contact the undersigned at (202) 942-6111 should any additional information be necessary for allowance.

Respectfully submitted,

Milan M Vinnola

David R. Marsh (Reg. No. 41,408)
Milan M. Vinnola (Reg. No. 45,979)

Date: April 29, 2003

ARNOLD & PORTER
555 Twelfth Street, NW
Washington, D.C. 20004
(202) 942-5000 telephone
(202) 942-5999 facsimile